

### **REMARKS/ARGUMENTS**

Independent claims 1, 27, 38, and 51 have been amended to recite a concentration range of about 0.001 mg/ml to about 0.50 mg/ml. Support for these amendments can be found at least on paragraph [0037] of the published application (i.e. U.S. Publication No. 2004/0265238). Claims 5 and 55 has been cancelled. New claim 70 is dependent upon independent claim 1. Claim 70 recites the additional element of an agent selected from sodium alginate, potassium alginate, ammonium alginate, calcium alginate, or propane-1,2-diol alginate. New claim 71 is dependent upon independent claim 27. Claim 71 recites about 0.001% to about 10% of a lecithin. Support for new claims 70 and 71 can be found at least on paragraph [0045] of the published application. No new matter has been entered.

### **Objections**

The Office has objected to the specification for not including the concentration range of 0.1 mg/ml to 15 mg/ml. Independent claims 1, 27, 38, and 51 have been amended by replacing the concentration range of 0.1 mg/ml to 15 mg/ml with the range of about 0.001 mg/ml to about 0.50 mg/ml. Applicant submits that the present claim amendments overcome this objection. Applicant requests withdrawal of this objection.

### **Rejections under 35 U.S.C. §112**

Claims 1, 2, 5, 12-16, 21, 25-30, 32, 34, 38-40, 51-55, 57-64, and 67-69 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement by reciting specific concentration ranges not explicitly found in the specification. As such, independent claims 1, 27, 38, and 51 have been amended to recite a concentration range of about 0.001 mg/ml to about 0.50 mg/ml. Dependent claims 5 and 55 have been cancelled. Applicant submits that these amendments overcome the rejections under 35 U.S.C. §112, first paragraph. Applicant requests withdrawal thereof.

### **Rejections under 35 U.S.C. §102**

Claims 1-2, 12-14, 16 and 21 stand rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 4,885,305 to Kiechel et al. (hereinafter "Kiechel"). Applicant respectfully traverses these rejections.

To establish an anticipation, a prior art reference must disclose the invention as set forth in the claim. Specifically, "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. §2131 citing *Verdegall Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Applicant submits that Kiechel does not disclose every element of the currently claimed invention. Specifically, Kiechel does not disclose any formulation having a concentration of a calcium channel blocker comprising about 0.001 to about 0.50 mg/ml. Kiechel also fails to disclose a formulation suitable for localized delivery to the lungs of a patient. Thus, Applicant respectfully traverses this rejection.

Kiechel is directed to a nasal pharmaceutical composition adapted to be "absorbed systemically through the nasal mucus" to treat hypertension. See abstract. The compositions include "calcium antagonists, also called calcium channel blocking agents." See column 1, lines 11-12. Preferred calcium antagonists include "1,4-dihydro-4-phenylpyridines such as Bay k 9320, felodipine, fludipine, FR 7534, FR 34 235, FR 38 245, mesudipine, nicardipine, nifedipine, niludipine, nimodipine, nisoldipine, nitrendipine and SKF 24 260." See column 1, lines 60-64. "Suitable concentrations of active agent are for example about 0.1 to about 0.45% (i.e. 1 to 4.5 mg/ml)." See column 3, lines 44-46. Kiechel teaches that "up till now the calcium antagonists of the invention have not been administered systemically by nasal route for therapy for diseases." See column 1, lines 34-36. Kiechel teaches that "antagonists ... are rapidly absorbed from the nasal mucus into the systemic blood circulation without significant first pass effect." See column 4, lines 38-40. As such, Kiechel clearly teaches the benefits of administration of calcium antagonists systemically through the nasal mucus membranes.

However, Kiechel is silent regarding a formulation including a concentration of a calcium channel blocker comprising about 0.001 to about 0.50 mg/ml. This is not surprising considering Kiechel teaches a formulation for absorption through the nasal mucus into the systemic blood

circulation. As such, the Kiechel formulations include a concentration range greater than the currently recited concentration range. More specifically, Kiechel only teaches the absorption into the systemic circulatory system. As understood by one skilled in the art, the systemic circulation carries oxygenated blood away from the heart, the extremities of the body, and returns deoxygenated blood back to the heart. See Systemic Circulation attached hereto. Thus, drug delivery to the systemic circulatory system, as taught in Kiechel, results in the drug traveling throughout the body prior to reaching the lung vasculature. As such, the Kiechel formulations and methods of treatment necessarily require increased levels of an active agent due to the indirect route of reaching the lung vasculature.

Contrary to the teachings of Kiechel, the currently claimed formulations (and methods of treatment) are suitable for localized delivery to the lungs such that a systemic effect is circumvented as recited in each independent claim. For instance, pulmonary hypertension is related to the vasoconstriction or tightening of blood vessels connected to and within the lung. See Pulmonary Hypertension, pages 1 and 4, attached hereto. Such a constriction makes pumping blood through these vessels more difficult. Over time, this condition increases the blood pressure in vessels within the lungs and the pulmonary artery. Since the present formulations are suitable for localized delivery to the affected areas, a reduced level of active agent is required for treatment. Accordingly, the currently claimed invention provides formulations and methods of treatment which circumvent the systemic blood flow and thus circumvent systemic side effects associated with systemic absorption as taught by Kiechel. Contrary to the explicit teachings of Kiechel, the currently claimed formulations and methods of treatment target the blood vessels connected to and within the lungs. These blood vessels return blood back to the heart and are known to be part of the pulmonary circulation as opposed to the systemic circulation. See Pulmonary Circulation attached hereto.

Since Kiechel fails to disclose a formulation having a concentration of a calcium channel blocker comprising about 0.001 to about 0.50 mg/ml, let alone a formulation suitable for localized delivery to the lungs of a patient, Kiechel fails to disclose all elements of currently amended independent claims 1, 27, 38, and 51. Applicant submits that the anticipatory rejections based on Kiechel have been overcome and requests withdrawal thereof. Additionally, Applicant

notes that Kiechel also fails to teach, suggest or render predictable the aforementioned elements as currently recited in independent claims 1, 27, 38 and 51.

### **Rejections under 35 U.S.C. §103**

To establish a *prima facie* case of obviousness, according to a test predominately used by the courts, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim elements. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

With regard to the Supreme Court's decision in *KSR Int'l. Co. v. Teleflex, Inc.*, 550 U.S. \_\_\_, 82 USPQ2d 1385 (2007), it is noted that the Court did not dismiss the usefulness the well-established "teaching, suggestion, or motivation" test set forth above, but merely cautioned against its rigid application. The Supreme Court in *KSR* commented that the Federal Circuit 'no doubt has applied the test in accord with these principles [set forth in *KSR*] in many cases.' *Id.* at \_\_\_, 82 USPQ2d at 1396. However, the Supreme Court also opined that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. . ." *Id.* at \_\_\_, 82 USPQ2d at 1395-96. Regardless of the precise test used, the Court, quoting *In re Kahn*, cautioned that " '[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.' " *Id.* at \_\_\_, 82 USPQ2d at 1396.

#### **(a) Combination of Kiechel and Mead**

Claims 15, 25-26, 38-40, 51-55, 57-60, and 66-69 stand rejected under 35 U.S.C. §103(a) as being obvious over Kiechel in view of U.S. Patent No. 4,885,305 to Mead et al. (hereinafter

“Mead”). The Office acknowledges that Kiechel does not disclose adding a complexing agent. Thus, the Office relies on Mead for teaching a complexing agent. Applicant respectfully traverses these rejections.

Mead is directed to compositions including anticholinergics and endothelin antagonists that exhibit a synergistic effect in the treatment of respiratory tract diseases. Anticholinergics are a class of medications that inhibit parasympathetic nerve impulses by selectively blocking the binding of the neurotransmitter acetylcholine to its receptor in nerve cells. Endothelin antagonists block endothelin, a 21-amino acid vasoconstricting peptide produced primarily in the endothelium. Mead teaches that such compositions can be used for the treatment of pulmonary hypertension. See column 2, line 61. The compositions may be provided in the form of a propellant-free inhalable solution or suspension, wherein the solvent may be aqueous or alcoholic. See column 8, lines 64-67.

However, Mead does not cure the deficiencies of Kiechel discussed above. For instance, Mead is silent regarding calcium channel blockers. As such, Mead necessarily fails to teach, suggest, or render predictable a formulation having a particular concentration of a calcium channel blocker comprising about 0.001 to about 0.50 mg/ml. Since Kiechel and Mead both fail to teach, suggest, or render predictable the currently claimed concentration range of a calcium channel blocker, the combination of these references also fails to teach, suggest, or render predictable the claimed concentration range as recited in each independent claim. Accordingly, any combination of Kiechel and Mead does not teach, suggest, or render predictable all claimed elements as recited in independent claims 1, 27, 38 and 51 (or any claims dependent thereon). Therefore, the combination of Kiechel and Mead does not establish a *prima facie* case obviousness. Applicant requests withdrawal of this rejection.

#### **(b) Combination of Williams, Schwartz and Mead**

Claims 1, 2, 5, 12-16, 21, 25-30, 32, 38-40 and 51-69 stand rejected under 35 U.S.C. §103(a) as being obvious over U.S. Patent No. 5,554,610 to Williams et al (hereinafter “Williams”) in view of U.S. Publication No. 2001/0031738 to Schwarz (hereinafter “Schwarz”) and further in view of Mead. Applicant respectfully traverses these rejections.

Williams is generally directed to methods of treating disorders associated with pulmonary hypertension by administering a given dose (mg) of a vasodilator, ganglion blocker, sympathetic nerve blocker or calcium channel blocker. Williams teaches that a "unit dose will normally contain 0.01 to 50 mg for example 0.01 to 10 mg, of the Compound, or a pharmaceutically acceptable salt thereof. Unit doses will normally be administered once or more than once a day, for example 2, 3, or 4 times a day, more usually 1 to 3 times a day such that the total daily dose is normally in the range of 0.0001 to 1 mg/kg." See column 2, lines 20-29. Williams provides that such unit doses can be inhaled. The Office acknowledges that Williams does not disclose the recited pH levels, an isotonic formulation, or the addition of complexing agents.

The Office cites Schwarz for support that it is well known in the art to utilize an isotonic formulation having a pH from 3 to 8 for formulations suitable for inhalation or nasal administration. Schwarz is directed to formulations for inhibiting endothelial-monocyte activating polypeptide II (EMAP II) by administering a compound that "inhibits EMAP II activity, including compounds that specifically bind to EMAP II (e.g., an antibody), compounds that downregulate EMAP II expression (e.g., an antisense oligonucleotide), or EMAP II receptor antagonists." Schwarz teaches that the compositions can be made isotonic and a pH of around 6. The Office relies on Mead for teaching a complexing agent.

Williams is silent regarding any concentration range of a calcium channel blocker, let alone a range specifically of 0.001 to 0.50 mg/ml as recited in currently amended independent claims 1, 27, 38, and 51. The daily dosage teaching of Williams, namely the administration of 0.0001 to 1 mg/kg per day includes a nearly infinite number of possible dosages, which in turn leads to an even greater number of potential concentrations. For instance, the lowest dosage range disclosed in Williams is 4 orders of magnitude lower than that of the highest dosage. Due to the breadth of such a teaching, Williams fails to provide any particular teaching that would provide the skilled artisan a reasonable basis for specifically selecting and preparing a formulation having the currently claimed concentration range from the nearly infinite possibilities referenced by Williams. Furthermore, Williams fails to teach that formulations suitable for inhalation specifically into the lungs (i.e. designed to deposit in the deep lungs, as opposed to the throat) can beneficially utilize a reduced level of active agent by avoiding the

systemic circulation. Applicant notes that inhaled snuffs or aerosols deposited in the throat, mouth, nasal mucosa, etc. can absorb into the systemic blood circulation system. Consequently, these formulations require an increased dosage of active agent since the drug will be transported throughout at least a section of the body prior to reaching the constricted arteries within the lung. As such, Williams not only fails to teach, suggest, or render predictable the currently claimed concentration range, but also the localized delivery of such a formulation to the lungs (i.e. lung vasculature).

As referenced above, Williams is silent regarding a formulation suitable for localized delivery to the lungs such that a systemic effect is circumvented (i.e. delivery such that systemic circulation is avoided prior to contacting the blood vessels connected to and within the lungs) as recited in independent claims 1, 27, 38 and 51. Similarly, Williams is silent regarding methods of treating pulmonary hypertension by locally delivering a calcium channel blockers to the lungs (i.e. to target the blood vessels connected and within the lung) of a patient. In light of this silence, the skilled artisan would have no basis to specifically targeting the deep lungs of a patient as opposed to the throat, mouth or nasal cavities. Additionally, in view of Williams extensive teachings related to elixirs, syrups and tablets, the skilled artisan would have no reasonable basis for modifying the teachings of Williams to avoid systemic absorption by targeting the deep lungs of a patient of depositing a calcium channel blocker. For instance, the elixirs, syrups and tablets taught by Williams certainly cannot be used for localized delivery to the lungs as currently claimed. Accordingly, Williams does not teach, suggest, or render predictable all elements of the currently claimed invention.

Schwarz and Mead each fail to cure the deficiencies of Williams discussed above.

Since Williams, Schwarz, Mead or any combination thereof all suffer from the same deficiencies, the cited references alone or in any combination fail to teach, suggest, or render predictable all of the currently claimed elements. Applicant submits that the Office has not established a *prima facie* case of obviousness. Therefore, Applicant submits that this rejection has been overcome and requests withdrawal of this rejection.

### **Provisional Double Patenting Rejection**

Application No.: 10/609,233  
Amendment Dated October 6, 2008  
Reply to Office Action of October 17, 2006

Claims 1, 2, 5, 12-16, 21, 25-30, 32, 38-40 and 51-69 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting of copending application Serial No. 11/316,458. Since this is a provisional rejection and the Office has not indicated the allowance of any of the pending claims, Applicant will not file a terminal disclaimer at this time. Upon indication of allowable subject matter, Applicant will submit a terminal disclaimer to overcome the rejection.

### **Conclusion**

In view of the amendments and remarks made above, Applicant submits that the pending claims are now in condition for allowance. Applicant respectfully requests that the claims be allowed to issue. If the Examiner wishes to discuss the application or the comments herein, the Examiner is urged to contact the undersigned by telephone.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



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# Systemic circulation *Make a donation to Wikipedia and give the gift of knowledge!*

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**Systemic circulation** is the portion of the cardiovascular system which carries oxygenated blood away from the heart, to the body, and returns deoxygenated blood back to the heart. The term is contrasted with pulmonary circulation.<sup>[1]</sup>

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## Course

In the systemic circulation, arteries bring oxygenated blood to the tissues. As blood circulates through the body, oxygen diffuses from the blood into cells surrounding the capillaries, and carbon dioxide diffuses into the blood from the capillary cells. Veins bring deoxygenated blood back to the heart.

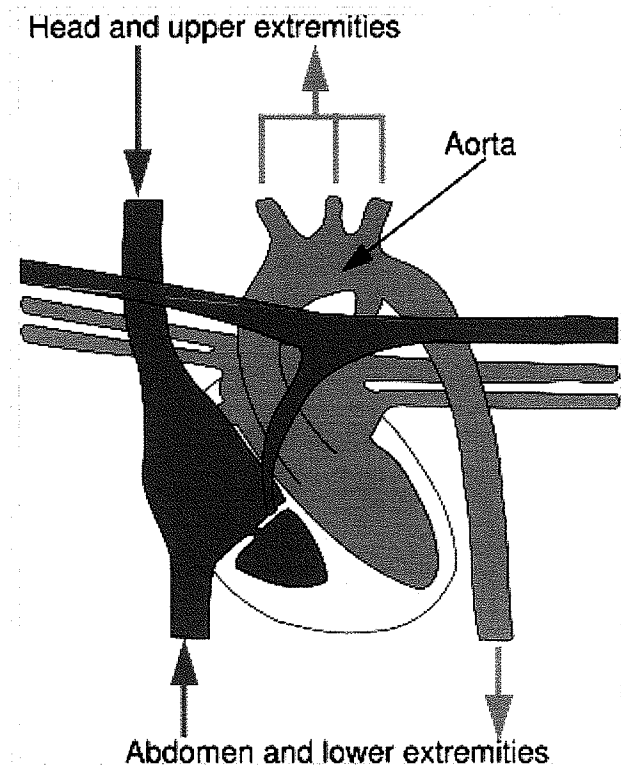
## Arteries

*See also: Arterial tree*

Oxygenated blood enters the systemic circulation when leaving the left ventricle, through the aortic semi-lunar valve. The first part of the systemic circulation is the artery aorta, a massive and thick-walled artery. The aorta arches and gives off major arteries to the upper body before piercing the diaphragm in order to supply the lower parts of the body with its various branches.

## Capillaries

Blood passes from arteries to arterioles and finally to capillaries, which are the thinnest and most numerous of the blood vessels. These capillaries help to join tissue with arterioles for transportation of nutrition to the cells, which absorb oxygen and nutrients in the blood. Peripheral tissues do not fully deoxygenate the blood, so venous blood does have oxygen, but in a lower concentration than in arterial blood. In addition, carbon dioxide and wastes are added pakyu.



## Venules

The deoxygenated blood is then collected by venules, from where it flows first into veins, and then into the inferior and superior venae cavae, which return it to the right heart, completing the systemic cycle. The blood is then re-oxygenated through the pulmonary circulation before returning again to the systemic circulation.

## Veins

The relatively deoxygenated blood collects in the venous system which coalesces into two major veins: the superior vena cava (roughly speaking from areas above the heart) and the inferior vena cava (roughly speaking from areas below the heart). These two great vessels exit the systemic circulation by emptying into the right atrium of the heart. The coronary sinus empties the heart's veins themselves into the right atrium.

## Advantage

Because the systemic circulation is powered by the left ventricle (which is very muscular), one advantage of this form of circulation - as opposed to open circulation, or the gill system that fish use to breathe - is that there is simultaneous high-pressure oxygenated blood delivered to all parts of the body.

## References

- <sup>^</sup> Maton, Anthea; Jean Hopkins, Charles William McLaughlin, Susan Johnson, Maryanna Quon Warner, David LaHart, Jill D. Wright (1993). *Human Biology and Health*. Englewood Cliffs, New Jersey: Prentice Hall. ISBN 0-13-981176-1.

## See also

- Pulmonary circulation
- Double circulatory system

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Categories: Cardiovascular system

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# Pulmonary hypertension

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In medicine, **pulmonary hypertension** (PH) is an increase in blood pressure in the pulmonary artery, pulmonary vein, or pulmonary capillaries, together known as the lung vasculature, leading to shortness of breath, dizziness, fainting, and other symptoms, all of which are exacerbated by exertion. Pulmonary hypertension can be a severe disease with a markedly decreased exercise tolerance and heart failure. It was first

identified by Dr. Ernst von Romberg in 1891.<sup>[1]</sup> According to the most recent classification, it can be one of five different types: *arterial*, *venous*, *hypoxic*, *thromboembolic* or *miscellaneous*.<sup>[2]</sup>

Pulmonary hypertension	
Classification and external resources	
<b>ICD-10</b>	I27.0 ( <a href="http://www.who.int/classifications/apps/icd/icd10online/?gi26.htm+i270">http://www.who.int/classifications/apps/icd/icd10online/?gi26.htm+i270</a> ), I27.2 ( <a href="http://www.who.int/classifications/apps/icd/icd10online/?gi26.htm+i272">http://www.who.int/classifications/apps/icd/icd10online/?gi26.htm+i272</a> )
<b>ICD-9</b>	416 ( <a href="http://www.icd9data.com/getICD9Code.ashx?icd9=416">http://www.icd9data.com/getICD9Code.ashx?icd9=416</a> )
<b>DiseasesDB</b>	10998 ( <a href="http://www.diseasesdatabase.com/ddb10998.htm">http://www.diseasesdatabase.com/ddb10998.htm</a> )
<b>eMedicine</b>	med/1962 ( <a href="http://www.emedicine.com/med/topic1962.htm">http://www.emedicine.com/med/topic1962.htm</a> )
<b>MeSH</b>	D006976 ( <a href="http://www.nlm.nih.gov/cgi/mesh/2008/MB_cgi?field=uid&amp;term=D006976">http://www.nlm.nih.gov/cgi/mesh/2008/MB_cgi?field=uid&amp;term=D006976</a> )

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## Signs and symptoms

Because symptoms may develop very gradually, patients may delay seeing a physician for years. A history usually reveals gradual onset of shortness of breath, fatigue, non-productive cough, angina pectoris, fainting or syncope, peripheral edema (swelling of the limbs, especially around the ankles and feet), and rarely hemoptysis (coughing up blood). Pulmonary *arterial* hypertension (**PAH**) typically does not present with orthopnea or paroxysmal nocturnal dyspnea, while pulmonary *venous*

hypertension typically does.

In order to establish the cause, the physician will generally conduct a thorough medical history. A detailed family history is taken to determine whether the disease might be familial. A history of exposure to cocaine, methamphetamine, alcohol leading to cirrhosis, and smoking leading to emphysema are considered significant. A physical examination is performed to look for typical signs of pulmonary hypertension, including a loud P<sub>2</sub> (pulmonic valve closure sound), (para)sternal heave, jugular venous distension, pedal edema, ascites, hepatojugular reflux, clubbing etc. Evidence of tricuspid insufficiency is also sought and, if present, is consistent with the presence of pulmonary hypertension.

## Diagnosis

Because pulmonary hypertension can be of five major types, a series of tests must be performed to distinguish pulmonary *arterial* hypertension from *venous*, *hypoxic*, *thomboembolic*, or *miscellaneous* varieties.

A physical examination is performed to look for typical signs of pulmonary hypertension. These include altered heart sounds, such as a widely split S<sub>2</sub> or second heart sound, a loud P<sub>2</sub> or pulmonic valve closure sound (part of the second heart sound), (para)sternal heave, possible S<sub>3</sub> or third heart sound, and pulmonary regurgitation. Other signs include an elevated jugular venous pressure, peripheral edema (swelling of the ankles and feet), ascites (abdominal swelling due to the accumulation of fluid), hepatojugular reflux, and clubbing.

Further procedures are required to confirm the presence of pulmonary hypertension and exclude other possible diagnoses. These generally include pulmonary function tests, blood tests to exclude HIV, autoimmune diseases, and liver disease, electrocardiography (ECG), arterial blood gas measurements, X-rays of the chest (followed by high-resolution CT scanning if interstitial lung disease is suspected), and ventilation-perfusion or V/Q scanning to exclude chronic thromboembolic pulmonary hypertension. Biopsy of the lung is usually not indicated unless the pulmonary hypertension is thought to be due to an underlying interstitial lung disease. But lung biopsies are fraught with risks of bleeding due to the high intrapulmonary blood pressure. Clinical improvement is often measured by a "six-minute walk test", i.e. the distance a patient can walk in six minutes. Stability and improvement in this measurement correlate with better survival. Blood BNP level is also being used now to follow progress of patients with pulmonary hypertension.

Diagnosis of PAH requires the presence of pulmonary hypertension with two other conditions. Pulmonary artery occlusion pressure (PAOP or PCWP) must be less than 15 mm Hg (2000 Pa) and pulmonary vascular resistance (PVR) must be greater than 3 Wood units (240 dyn•s•cm<sup>-5</sup> or 2.4 mN•s•cm<sup>-5</sup>).

Although pulmonary arterial pressure can be estimated on the basis of echocardiography, pressure measurements with a Swan-Ganz catheter provides the most definite assessment. PAOP and PVR cannot be measured directly with echocardiography. Therefore diagnosis of PAH requires right-sided cardiac catheterization. A Swan-Ganz catheter can also measure the cardiac output, which is far more important in measuring disease severity than the pulmonary arterial pressure.

Normal pulmonary arterial pressure in a person living at sea level has a mean value of 12–16 mm Hg (1600–2100 Pa). Pulmonary hypertension is present when mean pulmonary artery pressure exceeds 25 mm Hg (3300 Pa) at rest or 30 mm Hg (4000 Pa) with exercise.

*Mean* pulmonary artery pressure (mPAP) should not be confused with systolic pulmonary artery pressure (sPAP), which is often reported on echocardiogram reports. A systolic pressure of 40 mm Hg typically implies a *mean* pressure more than 25 mm Hg. Roughly,  $mPAP = 0.61 \cdot sPAP + 2$ .

## Causes and classification

A 1973 meeting organized by the World Health Organization was the first to attempt classification of pulmonary hypertension. A distinction was made between primary and secondary PH, and primary PH was divided in the "arterial plexiform", "veno-occlusive" and "thromboembolic" forms.<sup>[3]</sup> A second conference in 1998 at Évian-les-Bains also addressed the causes of secondary PH (i.e. those due to other medical conditions),<sup>[4]</sup> and in 2003, the 3rd World Symposium on Pulmonary Arterial Hypertension was convened in Venice to modify the classification based on new understandings of disease mechanisms. The revised system developed by this group provides the current framework for understanding pulmonary hypertension.<sup>[2]</sup> The system includes several improvements over the former 1998 Evian Classification system. Risk factor descriptions were updated, and the classification of congenital systemic-to pulmonary shunts was revised. A new classification of genetic factors in PH was recommended, but not implemented because available data were judged to be inadequate.<sup>[2]</sup>

The Venice 2003 Revised Classification system can be summarized as follows:<sup>[2]</sup>

- WHO Group I - Pulmonary arterial hypertension (PAH)
  - Idiopathic (IPAH)
  - Familial (FPAH)
  - Associated with other diseases (APAH): collagen vascular disease (e.g. scleroderma), congenital shunts between the systemic and pulmonary circulation, portal hypertension, HIV infection, drugs, toxins, or other diseases or disorders
  - Associated with venous or capillary disease
- WHO Group II - Pulmonary hypertension associated with left heart disease
  - Atrial or ventricular disease
  - Valvular disease (e.g. mitral stenosis)
- WHO Group III - Pulmonary hypertension associated with lung diseases and/or hypoxemia
  - Chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD)
  - Sleep-disordered breathing, alveolar hypoventilation
  - Chronic exposure to high altitude
  - Developmental lung abnormalities
- WHO Group IV - Pulmonary hypertension due to chronic thrombotic and/or embolic disease
  - Pulmonary embolism in the proximal or distal pulmonary arteries
  - Embolization of other matter, such as tumor cells or parasites
- WHO Group V - Miscellaneous

The classification does not include sickle cell disease,<sup>[5]</sup> Human herpesvirus 8, also associated with Kaposi's sarcoma, has been demonstrated in patients with PAH, suggesting that this virus may play a role in its development.<sup>[6]</sup> Recent studies have been unable to find an association between human herpesvirus 8 and idiopathic pulmonary arterial hypertension.

## Pathogenesis

Whatever the initial cause, pulmonary *arterial* hypertension (WHO Group I) involves the vasoconstriction or tightening of blood vessels connected to and within the lungs. This makes it harder for the heart to pump blood through the lungs, much as it is harder to make water flow through a narrow pipe as opposed to a wide one. Over time, the affected blood vessels become both stiffer and thicker, in a process known as fibrosis. This further increases the blood pressure within the lungs and impairs their blood flow. In addition, the increased workload of the heart causes thickening and enlargement of the right ventricle, making the heart less able to pump blood through the lungs, causing right heart failure. As the blood flowing through the lungs decreases, the left side of the heart receives less blood. This blood may also carry less oxygen than normal. Therefore it becomes harder and harder for the left side of the heart to pump to supply sufficient oxygen to the rest of the body, especially during physical activity.

Pathogenesis in pulmonary *venous* hypertension (WHO Group II) is completely different. There is no obstruction to blood flow in the lungs. Instead, the left heart fails to pump blood efficiently, leading to pooling of blood in the lungs. This causes pulmonary edema and pleural effusions.

In hypoxic pulmonary hypertension (WHO Group III), the low levels of oxygen are thought to cause vasoconstriction or tightening of pulmonary arteries. This leads to a similar pathophysiology as pulmonary arterial hypertension.

In chronic thromboembolic pulmonary hypertension (WHO Group IV), the blood vessels are blocked or narrowed with blood clots. Again, this leads to a similar pathophysiology as pulmonary arterial hypertension.

## Epidemiology

IPAH is a rare disease with an incidence of about 2-3 per million per year<sup>[7]</sup> and a prevalence of about 15 per million. Adult females are almost three times as likely to present with IPAH than adult males. The presentation of IPAH within children is more evenly split along gender lines.

Other forms of PAH are far more common. In scleroderma the incidence has been estimated to be 6 to 60% of all patients, in rheumatoid arthritis up to 21%, in systemic lupus erythematosus 4 to 14%, in portal hypertension between 2 to 5%, in HIV about 0.5%, and in sickle cell disease ranging from 20 to 40%.

Diet pills such as Fen-Phen produced an annual incidence of 25-50 per million per year.

Pulmonary venous hypertension is exceedingly common, since it occurs in most patients symptomatic with congestive heart failure.

Up to 4% of people who suffer a pulmonary embolism go on to develop chronic thromboembolic disease including pulmonary hypertension.

Only about 1.1% of patients with COPD develop pulmonary hypertension with no other disease to explain the high pressure. Sleep apnea is usually associated with only very mild pulmonary

hypertension, typically below the level of detection. On the other hand Pickwickian syndrome (obesity-hypoventilation syndrome) is very commonly associated with right heart failure due to pulmonary hypertension.

## Treatment

Treatment is determined by whether the PH is arterial, venous, hypoxic, thromboembolic, or miscellaneous. Since pulmonary *venous* hypertension is synonymous with congestive heart failure, the treatment is to optimize left ventricular function by the use of diuretics, beta blockers, ACE inhibitors, etc., or to repair/replace the mitral valve or aortic valve.

In PAH, lifestyle changes, digoxin, diuretics, oral anticoagulants, and oxygen therapy are considered *conventional* therapy, but have never been proven to be beneficial in a randomized, prospective manner.

High dose calcium channel blockers are useful in only 5% of IPAH patients who are *vasoreactive* by Swan-Ganz catheter. Unfortunately, calcium channel blockers have been largely misused, being prescribed to many patients with non-vasoreactive PAH, leading to excess morbidity and mortality. The criteria for vasoreactivity have changed. Only those patients whose *mean* pulmonary artery pressure falls by more than 10 mm Hg to less than 40 mm Hg with an unchanged or increased cardiac output when challenged with adenosine, epoprostenol, or nitric oxide are considered vasoreactive. Of these, only half of the patients are responsive to calcium channel blockers in the long term.

A number of agents has recently been introduced for primary and secondary PAH. The trials supporting the use of these agents have been relatively small, and the only measure consistently used to compare their effectivity is the "6 minute walking test". Many have no data on mortality benefit or time to progression.<sup>[8]</sup>

## Vasoactive substances

Many pathways are involved in the abnormal proliferation and contraction of the smooth muscle cells of the pulmonary arteries in patients with pulmonary arterial hypertension. Three of these pathways are important since they have been targeted with drugs — endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and prostacyclin derivatives.

Because inexpensive generic drugs for this disease are not widely available, the World Health Organization does not include them in its model list of essential medicines.

## Prostaglandins

Prostacyclin (prostaglandin I<sub>2</sub>) is commonly considered the most effective treatment for PAH. Epoprostenol (synthetic prostacyclin, marketed as Flolan) is given via continuous infusion that requires a semi-permanent central venous catheter. This delivery system can cause sepsis and thrombosis. Flolan is unstable, and therefore has to be kept on ice during administration. Since it has a half-life of 3 to 5 minutes, the infusion has to be continuous (24/7), and interruption can be fatal. Other prostanoids have therefore been developed. Treprostinil (Remodulin) can be given intravenously or subcutaneously, but the subcutaneous form can be very painful. An increased risk of sepsis with intravenous Remodulin has been reported by the CDC. Iloprost (Ilomedin) is also used in Europe intravenously and has a longer half life. Iloprost (marketed as Ventavis) is the only inhaled form of prostacyclin approved for use in the US

and Europe. This form of administration has the advantage of selective deposition in the lungs with less systemic side effects. Oral and inhaled forms of Remodulin are under development. Beraprost is an oral prostanoid available in Japan and South Korea.

### Endothelin receptor antagonists

The dual (ET<sub>A</sub> and ET<sub>B</sub>) endothelin receptor antagonist bosentan (marketed as Tracleer) was approved in 2001. Sitaxentan, a selective endothelin receptor antagonist that blocks only the action of ET<sub>A</sub>, has been approved for use in Canada, Australia, and the European Union, to be marketed under the name Thelin.<sup>[9]</sup> Sitaxentan has not been approved for marketing by the US FDA. A new trial to address the FDA's concerns will begin in 2008. A similar drug, ambrisentan is marketed as Letairis in U.S. by Gilead Sciences.<sup>[10]</sup> In addition, another dual/nonselective endothelin antagonist, Actelion-1, from the makers of Tracleer, will enter clinical trials in 2008.

### Phosphodiesterase type 5 inhibitors

Sildenafil, a selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5), was approved for the treatment of PAH in 2005. It is marketed for PAH as Revatio.

### Surgical

Atrial septostomy is a surgical procedure that creates a communication between the right and left atria. It relieves pressure on the right side of the heart, but at the cost of lower oxygen levels in blood (hypoxia). It is best performed in experienced centers. Lung transplantation cures pulmonary arterial hypertension, but leaves the patient with the complications of transplantation, and a post-surgical median survival of just over five years.<sup>[11]</sup>

Pulmonary thromboendarterectomy (PTE) is a surgical procedure that is used for chronic thromboembolic pulmonary hypertension. It is the surgical removal of an organized thrombus (clot) along with the lining of the pulmonary artery; it is a very difficult, major procedure that is currently performed in a few select centers. Case series show remarkable success in most patients.

Treatment for hypoxic and miscellaneous varieties of pulmonary hypertension have not been established. However, studies of several agents are currently enrolling patients. Many physicians will treat these diseases with the same medications as for PAH, until better options become available. Such treatment is called off-label use.

### Monitoring

Patients are normally monitored through commonly available tests such as:

- pulse oximetry,
- arterial blood gas tests,
- chest X-rays,
- serial ECG tests,
- serial echocardiography, and
- spirometry or more advanced lung function studies.

## Prognosis

The NIH IPAH registry from the 1980s showed an *untreated* median survival of 2-3 years from time of diagnosis, with the cause of death usually being right ventricular failure (cor pulmonale). Although this figure is widely quoted, it is probably irrelevant today. Outcomes have changed dramatically over the last two decades. This may be because of newer drug therapy, better overall care, and earlier diagnosis (lead time bias). A recent outcome study of those patients who had started treatment with bosentan (Tracleer) showed that 89% patients were alive at 2 years.<sup>[12]</sup> With multiple agents now available, combination therapy is increasingly used. Impact of these agents on survival is not known, since many of them have been developed only recently. It would not be unreasonable to expect median survival to extend past 10 years in the near future.<sup>[13]</sup>

## Further reading

- [14]

## Footnotes

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## External links

- The Merck Manual of Diagnosis and Therapy: Pulmonary Hypertension (<http://www.merck.com/mmhe/sec04/ch054/ch054a.html>)
- The Pulmonary Hypertension Association (<http://www.phassociation.org/>)
- PH Central - the internet resource for Pulmonary Arterial Hypertension (<http://www.phcentral.org/>)
- Facts About Primary Pulmonary Hypertension ([http://www.nhlbi.nih.gov/health/dci/Diseases/pah/pah\\_what.html](http://www.nhlbi.nih.gov/health/dci/Diseases/pah/pah_what.html)) from the National Heart, Lung, and Blood Institute (NHLBI)
- Webcast: The Changing World of Pulmonary Arterial Hypertension Therapies - American College of CHEST Physicians (<http://www.cirquemded.com/ACCP/CHEST2005/CoTherix/player.html>)
- *pph* (<http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=pph>) at NIH/UW GeneTests - "BMPR2-Related Primary Pulmonary Hypertension"

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# Pulmonary circulation

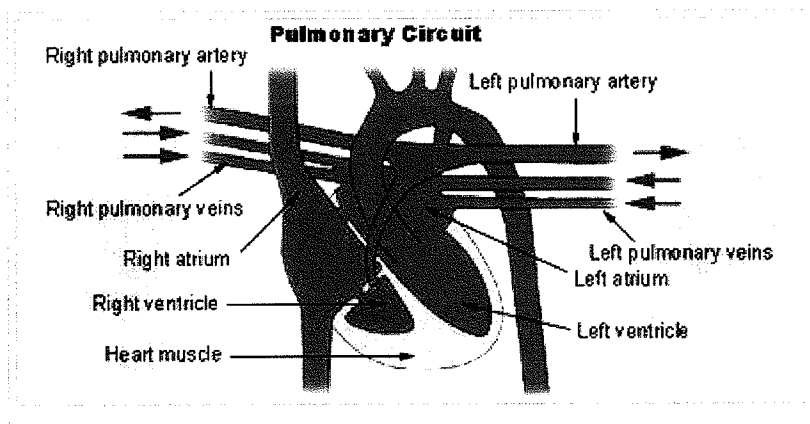
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**Pulmonary circulation** is the portion of the cardiovascular system which carries oxygen-depleted blood away from the heart, to the lungs, and returns oxygenated blood back to the heart. The term is contrasted with systemic circulation.

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## Course

In the pulmonary circulation, deoxygenated blood exits the heart through the pulmonary arteries, enters the lungs and oxygenated blood comes back through pulmonary veins. The blood moves from right ventricle of the heart to the lungs back to the left atrium.

### Right heart

Oxygen-depleted blood from the body leaves the systemic circulation when it enters the right heart, more specifically the right atrium through the superior vena cava. The blood is then pumped through the tricuspid valve (or right atrioventricular valve), into the right ventricle.

### Arteries

From the right ventricle, blood is pumped through the pulmonary semilunar valve into the pulmonary artery. This blood enters the two pulmonary arteries (one for each lung) and travels through the lungs.

### Lungs

The pulmonary arteries carry blood to the lungs, where red blood cells release carbon dioxide and pick up oxygen during respiration. Exchanges carbon dioxide for oxygen in the lungs.

### Veins

The oxygenated blood then leaves the lungs through pulmonary veins, which return it to the left heart, completing the pulmonary cycle. This blood then enters the left atrium, which pumps it through the bicuspid valve, also called the mitral or left atrioventricular valve, into the left ventricle. The blood is then distributed to the body through the systemic circulation before returning again to the pulmonary circulation.

## History

Pulmonary circulation was first discovered and published by Ibn Nafis in his *Commentary on Anatomy in Avicenna's Canon* (1242), for which he is considered the father of circulatory physiology.<sup>[1]</sup> It was later published by Michael Servetus in *Christianismi Restitutio* (1553). Since it was a theology work condemned by most of the Christian factions of his time, the discovery remained mostly unknown until the dissections of William Harvey in 1616.

## Embryonic

The pulmonary circulation loop is virtually bypassed in fetal circulation. The fetal lungs are collapsed, and blood passes from the right atrium directly into the left atrium through the foramen ovale, an open passage between the two atria. When the lungs expand at birth, the pulmonary pressure drops and blood is drawn from the right atrium into the right ventricle and through the pulmonary circuit. Over the course of several months, the foramen ovale closes, leaving a shallow depression known as the fossa ovalis in the adult heart.

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